Blood pressure variability in individuals with and without (pre)diabetes

Original Article

Blood pressure variability in individuals with and without (pre)diabetes: The Maastricht Study

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Objective: The mechanisms associating (pre)diabetes and cardiovascular disease (CVD) are incompletely understood. We hypothesize that greater blood pressure variability (BPV) may underlie this association, due to its association with (incident) CVD. Therefore, we investigated the association between (pre)diabetes and very short-term to mid-term BPV, that is within-visit, 24-h and 7-day BPV.

Methods: Cross-sectional data from The Maastricht Study [normal glucose metabolism (NGM), $n = 1924$; prediabetes, $n = 511$; type 2 diabetes mellitus (T2DM), $n = 975$; 51% men, aged 60 ± 8 years]. We determined SD for within-visit BPV ($n = 3244$), average real variability for 24-h BPV ($n = 2699$) day (0900–2100 h) and night (0100–0600 h) separately, and SD for 7-day BPV ($n = 2259$). Differences in BPV as compared with NGM were assessed by multiple linear regressions with adjustment for potential confounders.

Results: In T2DM, the average systolic/diastolic values of within-visit, 24-h and 7-day BPV were 4.8/2.6, 10.5/7.3 and 10.4/6.5 mmHg, respectively, and in prediabetes 4.9/2.6, 10.3/7.0 and 9.4/5.9 mmHg, respectively. T2DM was associated with greater nocturnal systolic BPV [0.42 mmHg (95% confidence interval: 0.05–0.80)], and greater 7-day systolic [0.76 mmHg (0.32–1.19)] and diastolic BPV [0.65 mmHg (0.29–1.01)], whereas prediabetes was associated with greater within-visit systolic BPV only [0.35 mmHg (0.06–0.65)], as compared with NGM.

Conclusion: Both T2DM and prediabetes are associated with slightly greater very short-term to mid-term BPV, which may, according to previous literature, explain a small part of the increased CVD risk seen in (pre)diabetes. Nevertheless, these findings do not detract from the fact that very short-term to mid-term BPV is substantial and important in individuals with and without (pre)diabetes.

Keywords: average real variability, blood pressure variability, cardiovascular diseases, diabetes mellitus, prediabetic state

Abbreviations: BPV, blood pressure variability; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NGM, normal glucose metabolism; T2DM, type 2 diabetes mellitus

INTRODUCTION

The mechanisms underlying the associations between type 2 diabetes (T2DM) and cardiovascular disease (CVD) are still only partially understood [1]. Importantly, the pathways linking T2DM to CVD are thought to be already present, to a somewhat lesser extent, in prediabetes [2]. A better understanding of these mechanisms is crucial, as it has been projected that, in 2025, 600 million individuals will suffer from T2DM, which will be followed by an epidemic of CVD [3].

Blood pressure (BP) variability (BPV), that is greater fluctuations of SBP or DBP at given mean pressures, has been shown to be associated with incident CVD independent of mean pressures [4] and thus may play a role in the association between (pre)diabetes and CVD. However, BPV in individuals with (pre)diabetes has not been systematically investigated, as previous studies have been relatively small [5–7], have targeted selected study populations [8,9], have used nonstandardized BP measurements [8,9] and/or have not adequately adjusted for the use of the various classes of antihypertensive medication [5–9], which may increase or decrease BPV depending on their therapeutic mechanism of action [10,11]. In addition, BPV in individuals with (pre)diabetes has not been systematically compared with that in individuals with normal glucose metabolism (NGM). The latter is important, because BP regulation in individuals with (pre)diabetes is known to differ from that in individuals with NGM in many ways [12], and these differences may increase BPV [13]. We therefore hypothesized that BPV may be greater in individuals with (pre)diabetes. Indeed, there is some evidence that this may be the case [5–9].

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In view of the above, we investigated very short-term to mid-term (i.e. within-visit, 24-h and 7-day) BPV in participants of The Maastricht Study, a large population-based cohort study in which individuals with T2DM have been oversampled [14].

METHODS

Study design and population

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously [14]. In brief, the study focuses on the cause, pathophysiology, complications and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. The current report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Data collection

Blood pressure measurements and determination of blood pressure variability

Within-visit BPV was derived from office BP measurements according to international standards [15]. In short, office BP measurements were performed with the use of an oscillometric device (705-IT; Omron Healthcare, Kyoto, Japan), in a seated position on the right arm by trained research assistants, after 10 min of rest. BP was measured three times consecutively, with a 1-min interval. BP readings were taken between 09:30 and 11:30 a.m. as part of the first investigational study visit [14]. Within-visit BPV was computed as the SD when at least two BP readings were available.

Twenty-four-hour BPV was derived from ambulatory BP measurements according to international standards [16]. In short, ambulatory BP measurements were performed with the use of an oscillometric device (WatchBP O3; Microlife, Widnau, Switzerland) on the nondominant arm. Between 0800 and 2300 h readings were taken every 15 min; between 2300 and 0800 h, the interval was set at 30 min. Average real variability was calculated as measurement of 24-h BPV. The average real variability is the sum of the absolute differences of consecutive BP measurements divided by the number of differences and therefore takes into account the time series variability [17]. The 24-h BPV was calculated when at least 14 valid BP differences during daytime and at least seven valid BP differences during night-time were available. In addition, day (between 0900 and 2100 h) and night (between 0100 and 0600 h) average real variability values were analyzed separately.

Seven-day BPV was derived from home BP measurements according to international standards [18]. In short, home BP measurements were performed by participants with the use of an oscillometric device (WatchBP Home; Microlife) for 7 consecutive days, after instruction by trained researchers. Participants were instructed to measure their BP after at least 5-min rest in a seated position in the morning before breakfast and in the evening after dinner on the nondominant arm. The device measured BP twice consecutively each reading, with a 1-min interval. As 7-day BPV variable, SD was computed when at least 15 BP readings were available.

Glucose metabolism status

To determine glucose metabolism status, all participants, except those who used insulin, underwent a standardized 2-h 75 g oral glucose tolerance test (OGTT) after an overnight fast. For safety reasons, participants with a fasting glucose level above 11.0 mmol/l, as determined by a finger prick, did not undergo the OGTT. For these individuals, fasting glucose level and information about diabetes medication were used to determine glucose metabolism status. Glucose metabolism status was defined according to the WHO 2006 criteria into NGM, prediabetes (impaired fasting glucose and/or impaired glucose tolerance) and T2DM [19]. Participants with type 1 diabetes or other forms of diabetes were excluded.

Covariates

Alcohol consumption, smoking status, history of CVD and physical activity were assessed by questionnaire. Alcohol consumption was defined as nonconsumer, low consumer ($\leq$7 alcoholic drinks/week for women; $\leq$14 alcoholic drinks/week for men) or high consumer (>7 alcoholic drinks/week for women; >14 alcohol drinks/week for men). Smoking status was categorized into never, former and current smoker. BMI, waist circumference, total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglycerides, fasting plasma glucose, postload glucose and glycosylated hemoglobin (HbA1c) were determined as described elsewhere [14]. Estimated glomerular filtration rate (eGFR) was computed with the Chronic Kidney Disease Epidemiology Collaboration formula, using serum creatinine and cystatin C [20]. Information on the use of lipid-modifying and/or antihypertensive medication, that is generic names, doses and frequencies, were collected during an in person medication interview.

Statistical analysis

All data were analyzed using IBM SPSS software version 23.0 for Windows (IBM Corp., Somers, New York, USA). Data are presented as n (%), mean $\pm$ SD or median [interquartile range (IQR)]. To test for baseline differences, one-way analysis of variance (with P for linear trend) or the Kruskal–Wallis test for normally and nonnormally distributed continuous variables respectively, and χ^2 test for categorical variables were used. Associations between prediabetes, T2DM and BPV (within-visit, 24-h and 7-day; systolic and diastolic) were examined with the use of multiple linear regression models. Model 1 was adjusted

for age and sex; model 2 was additionally adjusted for mean SBP or DBP (either from office, 24-h or 7-day BP measurements, as appropriate); model 3 was additionally adjusted for smoking status and alcohol consumption; model 4 was additionally adjusted for BMI, history of CVD, HDL-C, LDL-C, use of lipid-modifying medication, eGFR; and model 5 was additionally adjusted for antihypertensive medication classes (beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers and nonloop diuretics separately). These models were repeated in a series of additional analyses for within-visit BPV with coefficient of variation and maximum–minimum difference instead of SD, for 24-h BPV with weighted SD and weighted coefficient of variation [21] instead of average real variability, and for 7-day BPV with coefficient of variation and average real variability instead of SD. Further additional analyses were done with adjustments for waist circumference (instead of BMI), heart rate (HR), the actual number of BP measurements and physical activity as confounders. In addition, to test whether these associations were modified by sex, we used interaction terms between glucose metabolism status and sex in the fully adjusted models. A two-sided *P* value of less than 0.05 was considered statistically significant [22], except for the interaction analyses, in which we used *P* less than 0.10.

RESULTS

Study population

From the 3451 participants, 41 participants with type 1 diabetes or other forms of diabetes were excluded. Data on covariates were missing for three participants on BMI, for four participants on cholesterol values, for four on medication history, for 33 on eGFR, for 63 on smoking habits, for 69 on alcohol use and for 108 on history of prior CVD (not mutually exclusive). In addition, data on BPs were missing for four participants on office BP, for 363 participants on 24-h BP and for 976 participants on 7-day home BP (not mutually exclusive). In the remaining participants, 3244 participants had adequate office BP measurement data, 2699 participants had adequate 24-h ambulatory BP measurement data and 2259 participants had adequate 7-day home BP measurement data [not mutually inclusive (Fig. 1)]. Missing data on BP measurements were due to logistic and technical reasons (e.g. measurement failures). Participants with and without missing data did not differ with regard to their baseline clinical characteristics, except for smoking [participants with missing ambulatory BP measurement data were more often current smokers (18.0 vs. 13.0%)].

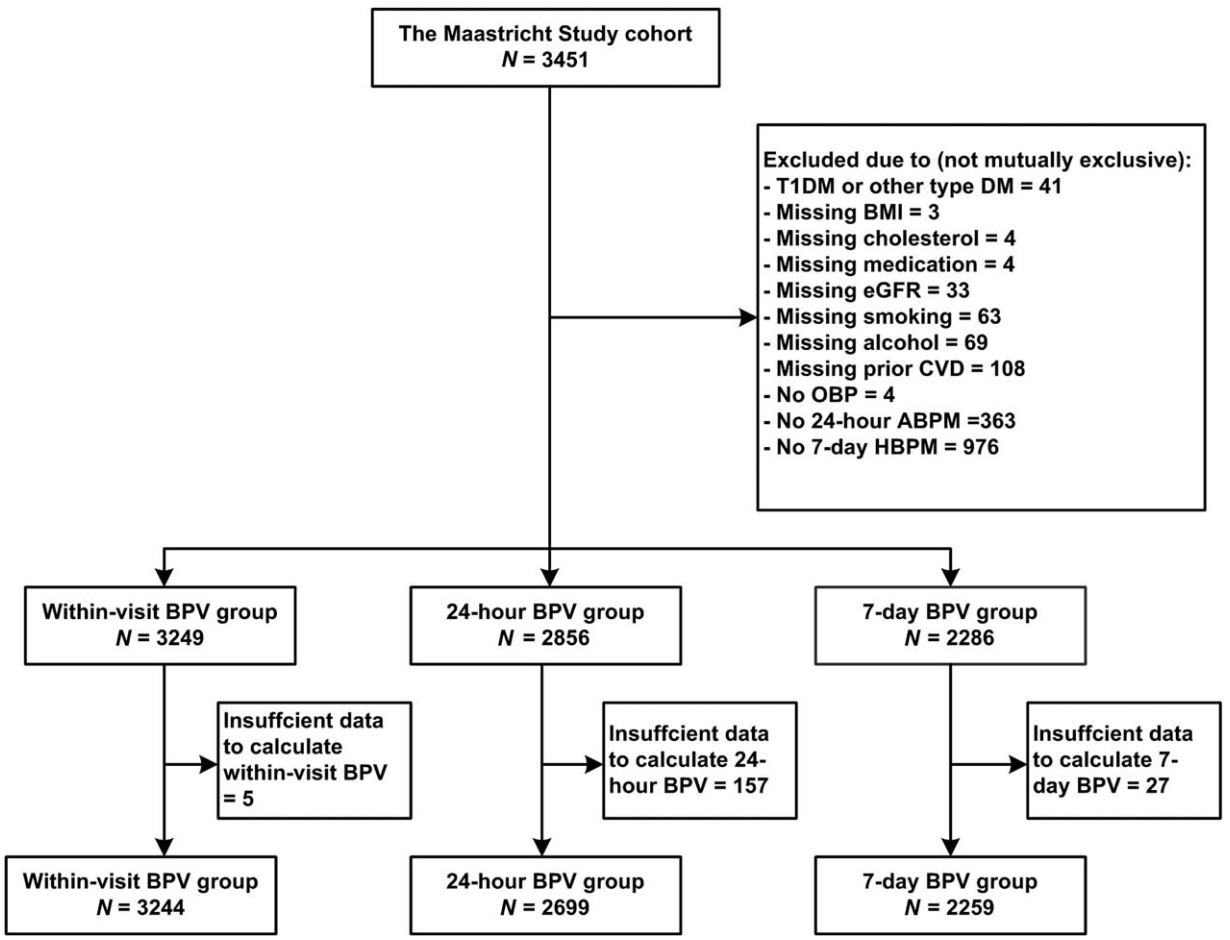

FIGURE 1 Flow diagram delineating the derivation of the final study population. ABPM, ambulatory blood pressure measurement; BPV, blood pressure variability; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration; HBPM, home blood pressure measurement; OBP, office blood pressure; T1DM, type 1 diabetes mellitus.

Characteristics of the study population

Tables 1 and 2 show characteristics of the within-visit BPV study population categorized according to glucose metabolism status. From NGM to T2DM, age, BMI, HbA1c, prior CVD and the use of lipid-modifying medication increased (P for trend <0.001); TC and LDL-C decreased (P for trend <0.001). The use of antihypertensive medication increased (P for trend <0.001), as did values of systolic, ambulatory and home BP measurements (P for trend <0.001). All calculated BPV variables, except for within-visit systolic BPV, increased from NGM to T2DM (P for trend <0.001–0.069). The characteristics of the within-visit, 24-h and 7-day BPV study populations were similar (Supplemental material Tables S1 and S2, http://links.lww.com/HJH/A838).

Associations between glucose metabolism status and blood pressure variability

Within-visit blood pressure variability

After adjustment for age, sex (model 1), mean SBP or DBP (model 2), smoking behavior and alcohol consumption (model 3), BMI, prior CVD, HDL-C, LDL-C, lipid-modifying medication, eGFR (model 4) and antihypertensive medication (model 5), only prediabetes was associated with statistically significantly greater within-visit systolic BPV as compared with NGM [regression coefficient (β) and 95% confidence interval]: 0.35 mmHg (0.06–0.65), whereas T2DM was not (Table 3, upper panel).

TABLE 1. Characteristics of the within-visit blood pressure variability study population

	NGM, $n = 1838$	Prediabetes, $n = 496$	T2DM, $n = 908$	P (trend)[a]
Age (years)	57.9 ± 8.2	61.5 ± 7.5	62.7 ± 7.7	<0.001
Men	797 (43.3%)	270 (54.4%)	620 (68.3%)	<0.001
Smoking behavior				<0.001
Never	719 (39.1%)	148 (29.8%)	257 (28.3%)	
Former	887 (48.2%)	286 (57.7%)	507 (55.8%)	
Current	233 (12.7%)	62 (12.5%)	144 (15.9%)	
Alcohol consumption				<0.001
None	249 (13.5%)	79 (15.9%)	275 (30.3%)	
Low	1073 (58.3%)	262 (52.8%)	457 (50.3%)	
High	517 (28.1%)	156 (31.3%)	176 (19.4%)	
History of cardiovascular disease	219 (11.9%)	69 (13.9%)	256 (28.2%)	<0.001
BMI (kg/m^2)	25.5 ± 3.6	27.8 ± 4.2	29.8 ± 5.0	<0.001
Waist circumference (cm)	90.5 ± 11.2	98.3 ± 12.4	105.8 ± 13.5	<0.001
MVPA (h/week)[b]	6.2 ± 4.5	5.1 ± 4.1	4.3 ± 4.0	<0.001
Total cholesterol (mmol/l)	5.6 ± 1.0	5.4 ± 1.1	4.4 ± 1.0	<0.001
HDL cholesterol (mmol/l)	1.7 ± 0.5	1.5 ± 0.4	1.3 ± 0.4	<0.001
LDL cholesterol (mmol/l)	3.4 ± 0.9	3.3 ± 1.0	2.4 ± 0.9	<0.001
Triglycerides (mmol/l)	1.06 (0.80–1.45)	1.35 (1.02–1.83)	1.53 (1.12–2.14)	<0.001
eGFR (ml/min per 1.73 m^2)	90.3 ± 13.2	86.7 ± 14.1	84.7 ± 17.1	<0.001
HbA1c (mmol/mol)[c]	36.0 ± 3.7	38.8 ± 4.5	52.1 ± 11.6	<0.001
Fasting plasma glucose (mmol/l)[d]	5.2 ± 0.4	5.9 ± 0.6	7.9 ± 2.0	<0.001
Postload glucose (mmol/l)[e]	5.4 ± 1.1	8.1 ± 1.7	14.3 ± 3.8	<0.001
Use of antidiabetic medication	–	–	711 (78.3%)	
Oral antidiabetics	–	–	663 (73.0%)	
Insulin	–	–	194 (21.4%)	
Use of lipid-modifying medication	303 (16.5%)	175 (35.3%)	679 (74.8%)	<0.001
Use of antihypertensive medication	408 (22.2%)	224 (45.2%)	654 (72.0%)	<0.001
Beta-blockers	165 (9.0%)	105 (21.2%)	308 (33.9%)	<0.001
Calcium channel blockers	66 (3.6%)	38 (7.7%)	192 (21.1%)	<0.001
ACE inhibitors	101 (5.5%)	46 (9.3%)	238 (26.2%)	<0.001
Angiotensin II receptor blockers	177 (9.6%)	111 (22.4%)	301 (33.1%)	<0.001
Diuretics	125 (6.8%)	94 (19.0%)	305 (33.6%)	<0.001
Blood pressure measurements				
Mean office SBP (mmHg)	130.7 ± 17.2	137.5 ± 17.0	142.3 ± 18.1	<0.001
Mean office DBP (mmHg)	75.2 ± 9.9	78.1 ± 9.6	77.3 ± 9.7	<0.001
Mean 24-h SBP (mmHg)[f]	118.7 ± 11.2	122.5 ± 11.9	123.6 ± 12.2	<0.001
Mean 24-h DBP (mmHg)[f]	75.3 ± 7.2	76.2 ± 7.1	74.3 ± 7.2	0.010
Mean home SBP (mmHg)[g]	124.0 ± 12.8	128.7 ± 12.3	133.5 ± 13.4	<0.001
Mean home DBP (mmHg)[g]	77.0 ± 8.5	78.0 ± 7.7	77.8 ± 7.9	0.029

Data are presented as n (%), mean ± SD or median (IQR). eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; MVPA, moderate-to-vigorous physical activity; NGM, normal glucose metabolism; T2DM, type 2 diabetes mellitus.
[a]P (Trend) for comparing linear trends across participants with normal glucose metabolism, prediabetes and T2DM were calculated with one-way ANOVA for normally distributed variables, the Kruskal–Wallis test for nonnormally disturbed variables and the χ^2 test for categorical variables.
[b]Available in 2834 participants ($n = 1647$ for NGM, $n = 439$ for prediabetes, $n = 748$ for T2DM).
[c]Available in 3231 participants ($n = 1933$ for NGM, $n = 439$ for prediabetes, $n = 905$ for T2DM).
[d]Available in 3241 participants ($n = 1838$ for NGM, $n = 496$ for prediabetes, $n = 907$ for T2DM).
[e]Available in 3011 participants ($n = 1834$ for NGM, $n = 494$ for prediabetes, $n = 683$ for T2DM).
[f]Values shown for 24-h BPV study population ($n = 1535$ for NGM, $n = 411$ for prediabetes, $n = 753$ for T2DM).
[g]Values shown for 7-day BPV study population ($n = 1270$ for NGM, $n = 337$ for prediabetes, $n = 652$ for T2DM).

TABLE 2. Within-visit, 24-h and 7-day blood pressure variability according to glucose metabolism status

	NGM, $n = 1839$	Prediabetes, $n = 496$	T2DM, $n = 908$	P (trend)[a]
Within-visit BPV				
SD_{SBP} (mmHg)	4.48 ± 2.76	4.93 ± 2.98	4.82 ± 3.08	0.001
SD_{DBP} (mmHg)	2.46 ± 1.62	2.59 ± 1.73	2.62 ± 1.93	0.013
24-h BPV	($n = 1535$)	($n = 411$)	($n = 753$)	
ARV_{SBP} (mmHg)	9.73 ± 2.37	10.27 ± 2.58	10.50 ± 2.51	<0.001
Day (0900–2100 h)	10.29 ± 3.25	10.62 ± 3.33	10.66 ± 3.23	0.008
Night (0100–0600 h)	8.84 ± 3.34	9.40 ± 3.29	10.20 ± 3.76	<0.001
ARV_{DBP} (mmHg)	6.85 ± 1.72	7.02 ± 1.80	7.25 ± 2.01	<0.001
Day (0900–2100 h)	7.13 ± 2.61	7.23 ± 2.72	7.34 ± 2.79	0.069
Night (0100–0600 h)	6.46 ± 2.63	6.78 ± 2.91	7.13 ± 3.13	<0.001
7-day home BPV	($n = 1270$)	($n = 337$)	($n = 652$)	
SD_{SBP} (mmHg)	8.76 ± 3.57	9.37 ± 3.40	10.43 ± 4.39	<0.001
SD_{DBP} (mmHg)	5.55 ± 2.78	5.89 ± 2.47	6.49 ± 3.67	<0.001

Data are presented as mean ± SD. ANOVA, analysis of variance; ARV, average real variability; NGM, normal glucose metabolism; T2DM, type 2 diabetes mellitus.
[a]P (trend) for comparing linear trends across participants with normal glucose metabolism, prediabetes and T2DM were calculated with one-way ANOVA.

TABLE 3. Associations between glucose metabolism status and within-visit, 24-h and 7-day blood pressure variability

	NGM (ref) β (95% CI)	Prediabetes β (95% CI)	T2DM β (95% CI)
Within-visit BPV			
SD_{SBP} (mmHg)			
Model 1	–	**0.37 (0.08–0.66)**	**0.26 (0.01–0.50)**
Model 2	–	0.26 (−0.03 to 0.54)	0.05 (−0.20 to 0.29)
Model 3	–	0.26 (−0.03 to 0.55)	0.04 (−0.21 to 0.28)
Model 4	–	**0.36 (0.07–0.66)**	0.23 (−0.07 to 0.53)
Model 5	–	**0.35 (0.06–0.65)**	0.26 (−0.04 to 0.56)
SD_{DBP} (mmHg)			
Model 1	–	0.09 (−0.09 to 0.26)	0.10 (−0.05 to 0.26)
Model 2	–	0.04 (−0.14 to 0.21)	0.07 (−0.07 to 0.21)
Model 3	–	0.04 (−0.14 to 0.21)	0.04 (−0.09 to 0.20)
Model 4	–	0.07 (−0.11 to 0.25)	0.14 (−0.04 to 0.32)
Model 5	–	0.05 (−0.13 to 0.23)	0.10 (−0.08 to 0.28)
24-h BPV			
ARV_{SBP} (mmHg)			
Model 1	–	**0.42 (0.15–0.68)**	**0.68 (0.46–0.90)**
Model 2	–	0.24 (−0.01 to 0.49)	**0.54 (0.33–0.75)**
Model 3	–	0.23 (−0.02 to 0.48)	**0.50 (0.28–0.71)**
Model 4	–	0.03 (−0.22 to 0.28)	0.15 (−0.10 to 0.40)
Model 5	–	0.02 (−0.23 to 0.28)	0.14 (−0.11 to 0.39)
ARV_{DBP} (mmHg)			
Model 1	–	0.12 (−0.08 to 0.32)	0.36 (0.19–0.53)
Model 2	–	0.07 (−0.13 to 0.27)	0.42 (0.25–0.58)
Model 3	–	0.07 (−0.13 to 0.26)	0.38 (0.21–0.55)
Model 4	–	−0.09 (−0.29 to 0.11)	0.07 (−0.13 to 0.27)
Model 5	–	−0.10 (−0.30 to 0.10)	0.06 (−0.15 to 0.26)
7-day home BPV			
SD_{SBP} (mmHg)			
Model 1	–	0.41 (−0.05 to 0.87)	**1.42 (1.04–1.80)**
Model 2	–	0.08 (−0.35 to 0.51)	**0.68 (0.32–1.04)**
Model 3	–	0.06 (−0.37 to 0.49)	**0.69 (0.32–1.06)**
Model 4	–	0.13 (−0.31 to 0.57)	**0.79 (0.35–1.22)**
Model 5	–	0.06 (−0.37 to 0.50)	**0.76 (0.32–1.19)**
SD_{DBP} (mmHg)			
Model 1	–	0.29 (−0.08 to 0.66)	**0.87 (0.57–1.17)**
Model 2	–	0.19 (−0.16 to 0.55)	**0.84 (0.55–1.13)**
Model 3	–	0.18 (−0.18 to 0.54)	**0.83 (0.53–1.13)**
Model 4	–	0.17 (−0.19 to 0.53)	**0.69 (0.33–1.04)**
Model 5	–	0.12 (−0.24 to 0.48)	**0.65 (0.29–1.01)**

Multiple linear regression analyses comparing differences in within-visit, 24-h and 7-day BPV between individuals with (pre)diabetes and normal glucose metabolism. Model 1 adjusted for age and sex; model 2 additionally adjusted for mean SBP or DBP (where appropriate); model 3: additionally adjusted for alcohol abuse and smoking behavior; model 4: additionally adjusted for BMI, prior CVD, HDL, LDL, lipid-lowering medication and eGFR; model 5: additionally adjusted for classes of antihypertensive medication. Bold values denote statistically significant associations. There were 3244 individuals (1535 with NGM, 496 with prediabetes, 908 with T2DM) included in the analyses between within-visit BPV and (pre)diabetes, 2699 individuals (1535 with NGM, 411 with prediabetes, 753 with T2DM) included in the analyses between 24-h BPV and (pre)diabetes, 2259 individuals (1270 with NGM, 337 with prediabetes, 625 with T2DM) included in the analyses between 7-day BPV and (pre)diabetes. ARV, average real variability; CI, confidence interval; NGM, normal glucose metabolism; T2DM, type 2 diabetes mellitus.

Both prediabetes and T2DM were not statistically significantly associated with within-visit diastolic BPV as compared with NGM (Table 3, upper panel).

Twenty-four-hour blood pressure variability

After adjustment for the covariates of the models 1–3, T2DM, but not prediabetes, was associated with greater 24-h systolic BPV as compared with NGM [0.50 mmHg (0.28–0.71)]. These results were attenuated and not statistically significant after further adjustment for the covariates of model 4 [0.15 mmHg (−0.13 to 0.27)] or model 5 [0.14 mmHg (−0.11 to 0.39)] (Table 3, middle panel). The attenuating effect seen between models 3 and 4 was mainly caused by adding BMI in model 4.

After adjustment for the covariates of the models 1–3, only T2DM, but not prediabetes, was associated with greater 24-h diastolic BPV as compared with NGM [0.38 mmHg (0.21–0.55)]. These results were attenuated and not statistically significant after further adjustment for the covariates of model 4 [0.07 mmHg (−0.13 to 0.27)] or model 5 [0.06 mmHg (−0.15 to 0.26)] (Table 3, middle panel). Again, the attenuating effect seen between models 3 and 4 was mainly caused by adding BMI in model 4.

If we analyzed daytime and night-time BPV separately, only T2DM was associated with greater nocturnal systolic BPV after adjustment for the covariates of the models 1–5 as compared with NGM [0.42 mmHg (0.05–0.80)] (Table 4).

Seven-day blood pressure variability

After adjustment for the covariates of the models 1–3, only T2DM, but not prediabetes, was associated with greater 7-day systolic BPV as compared with NGM [0.69 mmHg (0.32–1.06)]. This association became somewhat stronger after further adjustment for the covariates of model 4 [0.79 mmHg (0.35–1.22)] and model 5 [0.76 mmHg (0.32–1.19)].

After adjustment for the covariates of the models 1–3, only T2DM, but not prediabetes, was associated with greater 7-day diastolic BPV as compared with NGM [0.83 mmHg (0.53–1.13)]. This association was somewhat attenuated after further adjustment for the covariates of model 5 [0.65 mmHg (0.29–1.01)].

Additional analyses

After additional adjustment for waist circumference (instead of BMI), HR, the actual number of BP measurements and physical activity, the results did not materially change (Supplemental material Tables S3–S6, http://links.lww.com/HJH/A838).

If we repeated the analyses for within-visit BPV with coefficient of variation and the difference between maximum and minimum BP, and for 24-h BPV with weighted SD and weighted coefficient of variation, and for 7-day BPV with average real variability and coefficient of variation, the results were not materially changed (Supplemental material Tables S7–S9, http://links.lww.com/HJH/A838).

TABLE 4. Associations between glucose metabolism status and blood pressure variability during daytime and night-time as estimated from ambulatory blood pressure measurements

	NGM (ref) β (95% CI)	Prediabetes β (95% CI)	T2DM β (95% CI)
24-h BPV, day only			
ARV_{SBP} (mmHg)			
Model 1	–	0.28 (−0.07 to 0.63)	**0.44 (0.15–0.73)**
Model 2	–	0.12 (−0.22 to 0.45)	**0.36 (0.08–0.64)**
Model 3	–	0.10 (−0.24 to 0.44)	**0.29 (0.01–0.58)**
Model 4	–	−0.10 (−0.44 to 0.24)	−0.08 (−0.42 to 0.26)
Model 5	–	−0.09 (−0.43 to 0.25)	−0.06 (−0.41 to 0.29)
ARV_{DBP} (mmHg)			
Model 1	–	0.12 (−0.17 to 0.42)	**0.28 (0.04–0.53)**
Model 2	–	0.06 (−0.23 to 0.35)	**0.39 (0.14–0.63)**
Model 3	–	0.05 (−0.24 to 0.34)	**0.32 (0.07–0.57)**
Model 4	–	−0.14 (−0.43 to 0.16)	−0.04 (−0.34 to 0.25)
Model 5	–	−0.13 (−0.43 to 0.16)	−0.06 (−0.36 to 0.24)
24-h BPV, night only			
ARV_{SBP} (mmHg)			
Model 1	–	0.36 (−0.01 to 0.73)	**1.07 (0.76–1.38)**
Model 2	–	0.27 (−0.10 to 0.64)	**0.82 (0.51–1.13)**
Model 3	–	0.27 (−0.10 to 0.64)	**0.85 (0.54–1.17)**
Model 4	–	0.01 (−0.36 to 0.38)	**0.42 (0.04–0.79)**
Model 5	–	−0.01 (−0.38 to 0.36)	**0.42 (0.05–0.80)**
ARV_{DBP} (mmHg)			
Model 1	–	0.20 (−0.11 to 0.50)	**0.44 (0.18–0.69)**
Model 2	–	0.15 (−0.16 to 0.45)	**0.42 (0.16–0.67)**
Model 3	–	0.14 (−0.17 to 0.44)	**0.40 (0.14–0.66)**
Model 4	–	−0.07 (−0.38 to 0.24)	−0.03 (−0.34 to 0.28)
Model 5	–	−0.09 (−0.41 to 0.22)	−0.07 (−0.38 to 0.25)

Multiple linear regression analyses comparing differences in daytime and night-time BPV between individuals with (pre)diabetes and normal glucose metabolism. Model 1: adjusted for age and sex; model 2: additionally adjusted for mean SBP or DBP (where appropriate); model 3: additionally adjusted for alcohol abuse and smoking behavior; model 4: additionally adjusted for BMI, prior CVD, HDL, LDL, lipid-lowering medication and eGFR; and model 5: additionally adjusted for classes of antihypertensive medication. Bold values denote statistically significant associations. There were 2766 individuals (1563 with NGM, 426 with prediabetes, 777 with T2DM) included in the analyses between day BPV and (pre)diabetes, 2790 individuals (1586 with NGM, 424 with prediabetes, 780 with T2DM) included in the analyses between nocturnal BPV and (pre)diabetes. ARV, average real variability; CI, confidence interval; NGM, normal glucose metabolism; T2DM, type 2 diabetes mellitus.

Sex was an effect modifier in some of the associations between glucose metabolism status and BPV, but not all: the associations between prediabetes, and systolic within-visit and 7-day BPV were weaker in women, whereas the associations between prediabetes and T2DM, and systolic 24-h BPV were stronger in women. For both day and night, the association between T2DM and systolic BPV was stronger in women (details presented in Supplemental material Table S10, http://links.lww.com/HJH/A838).

Further analyses into antihypertensive medication and class effects on BPV [10] were hampered by a severe loss of statistical power (data not shown).

DISCUSSION

The current study had two main findings. First, the average systolic/diastolic values of within-visit, 24-h and 7-day BPV in our study population were substantial: 4.8/2.6, 10.5/7.3 and 10.4/6.5 mmHg, respectively, in individuals with T2DM, and 5.0/2.6, 10.3/7.0 and 9.4/5.9 mmHg, respectively, in individuals with prediabetes. Second, these values were, after adjustment for potential confounders, slightly larger than those in individuals with NGM. Specifically, T2DM was associated with significantly greater nocturnal systolic BPV and greater 7-day systolic and diastolic BPV, whereas prediabetes was associated with significantly greater within-visit systolic BPV only. According to previous literature, the slightly greater very short-term to mid-term BPV seen in (pre)diabetes corresponds to a relatively modest ~4% increased risk of cardiovascular events over an observation period of 5–7 years (e.g. an increase from 9.0 to 9.4%) [23,24], on the assumption that there is no interaction (synergy) between (pre)diabetes and very short-term to mid-term BPV. However, the average very short-term to mid-term BPV values we observed are in agreement with previous studies, which have shown that very short-term to mid-term BPV plays an important role in incident CVD [4,23,24]. Thus, these findings suggest that very short-term to mid-term BPV may, at most, explain a small part of the increased CVD risk seen in (pre)diabetes, but it does not detract from the fact that, regardless of the presence of (pre)diabetes, very short-term to mid-term BPV is substantial and important.

Previous studies on BPV in (pre)diabetes have not yielded consistent results. Two large Asian population-based studies did not present numerical values of differences in BPV values between individuals with (pre)diabetes and NGM [8,9], and one study [8] investigated associations with new-onset diabetes only. In addition, two relatively small studies [5,6] showed large differences in BPV, up to 3.7 mmHg, between individuals with (pre)diabetes and NGM, but did not adjust for potential confounders, such as age, mean BPs or the use of various classes of antihypertensive medication [5,6]. Hence, the results of the current study, in a population-based cohort enriched with individuals with T2DM, add to the existing literature by presenting accurate (differences in) BPV estimates, as we adhered to international guidelines on BP measurements [15,16,18] and were able to adjust for a large number of potential confounders.

The slightly greater very short-term to mid-term BPV in individuals with (pre)diabetes may be related to several factors, such as impaired baroreflex sensitivity caused by arterial carotid stiffening [25–27], and overactivity of the sympathetic nervous system caused by obesity [28] and/or (undiagnosed) sleep disordered breathing [29–31]. Further study is required to test these hypotheses.

Previous studies have suggested that in the presence of T2DM, CVD risk increases more in women as compared with men [32]. Our results, however, showed no clear pattern with regard to greater in BPV in women with (pre)diabetes, and these findings may represent the play of chance.

A major strength of the current report is the precise measurement of BPV estimates. In addition, OGTT-based classification of glucose metabolism status and the oversampling of individuals with T2DM enabled sufficient statistical power to accurately estimate BPV in (pre)diabetes. Also, we were able to adjust for an extensive range of covariates, including the use of various classes of antihypertensive medication. In fact, this may have led to some overadjustment, as, for instance, decreased renal function may lie in the causal pathway between (pre)diabetes and greater BPV. Consequently, we may, to some extent, have underestimated differences in BPV between individuals with (pre)diabetes and NGM [33]. Therefore, the true association will lie between model 3, in which only true confounders were added, and model 4. Even so, however, model 3 still shows that differences in BPV between individuals with (pre)diabetes and NGM are relatively modest. On the other hand, it should be emphasized that these modest differences were obtained in a study population that was well treated with regard to BP. Importantly, the latter implies that BPV-associated risk of CVD in (pre)diabetes can be reduced to approximately the same level as in individuals with NGM.

The current study had some further limitations. First, in light of the above, the generalizability of our results may be limited to white populations and those who had access to high-quality hypertension care. Second, due to the cross-sectional design of the study, any causal inference should be made with caution. Third, data on long-term BPV, that is visit-to-visit BPV, were unavailable. Visit-to-visit BPV has been strongly associated with incident CVD [34], and is a distinct type of BPV, as its underlying mechanisms are different from those of other types of BPV and include aging and seasonal climatic changes [35]. Hence, long-term BPV is not interchangeable with (very) short-term BPV [4,36].

In conclusion, individuals with (pre)diabetes have a slightly greater very short-term to mid-term BPV than those with NGM, which may explain a small part of the increased CVD risk seen in (pre)diabetes. Despite these small differences, very short-term to mid-term BPV remains substantial and important in individuals with and without (pre)diabetes. The results of the current study imply that greater very short-term to mid-term BPV may need to be considered as an important, treatable risk factor for CVD, regardless of glucose metabolism status. In addition, these results may also imply that when hypertension is well controlled, as is the case in our study population, the BPV-associated risk on CVD in (pre)diabetes may be reduced to approximately the same level as in individuals with NGM. Future research should explore whether the same applies to long-term BPV, that is visit-to-visit BPV, in individuals with and without (pre)diabetes.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Reviewer 2

The study examined short-term and long-term measures of BP variability in over 3000 normal patients and those with prediabetes and diabetes. The strength of the analysis employed is the multiple linear regression with adjustment for potential confounders and included five different models. The main findings were that greater nocturnal systolic blood pressure variability and greatest seven-day systolic variability and diastolic variability in patients with diabetes compared to normal subjects. By contrast, prediabetic's were associated with a greater within visit systolic blood pressure variability only. It must be said that differences between the three groups were relatively small and whether this is enough to predict increased cardiovascular risk would need to be determined in the long-term.